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Research Article

In silico ADME-Toxicity Profiling, Prediction of Bioactivity and CNS Penetrating Properties of some Newer Resveratrol Analogues

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Abstract

In silico ADME Toxicity profiling showed an interesting results against the resveratrol and its designed ligands (D1-D16), that these ligands were permeable by intestinal (Human Colonic Carcioma Cell Line) CaCo2 cell line and D8, D9, D11, D13, D14, D15, D16 were inhibitor of CYP2C19 microsomal enzyme which were may be active against breast cancer cell line, as the D13, D16 were belong to the p- glycoprotein substrate so there was a chance of efflux in the case of absorption. As well as the toxicity profile checked against the estrogen and androgen receptor, mutagenicity, carcinogenicity, human ether a gogo cell line, LD_{50} value clarifies the basic picture of potency. As the detail mechanism of resveratrol was not revealed, so the bioactivity profiling navigate the mechanism behind activity and finally the polar surface area, Log PS and Log BB value justify that molecule D1 was the better molecule which can cross the blood brain barrier. As well as there is a good correlation occurred in between Log P and Log PS with the r^2 value 0.7104 which can correlate with the brain penetration capacity of a molecule.

Keywords: Resveratrol analogue, ADME-toxicity, Bioactivity prediction, PSA, Log BB, Log PS

1.Introduction

Resveratrol (3, 4', 5-trihydroxy-trans-stilbene) is a phytoalexin found mainly in the skin of grapes and red wine and demonstrates anti-inflammatory, cardiovascular protective, and cancer chemopreventive properties.[1] There were some previous development occurred with the insertion of hydroxyl group with the phenyl group, insertion of hydroxymethyl group along with the azo stilbene , insertion of diethyl stilbene group as well as fewer derivatives with fluorine, para hydroxy phenyl, insertion of dimethyl amino groups with diversified activity against COX-1, COX-2 and NFK-β inhibitor.[2-5] Resveratrol has been found to inhibit the proliferation of several kinds of tumors such as leukemia, prostate, breast and colon cancers.[6–10] In preclinical study Sheng-Hong Tseng et al suggest that resveratrol could suppresses the growth of gliomas in rat.[11] In present study we have designed some Resveratrol analogue on basis of their physicochemical parameter and predict that weather these could target brain tumor like glioma. Due to its diversified activity profile this molecule draw the attention of the researcher to develop its newer analogue. So in this present study, our main intention is to develop a series of *in silico* resveratrol analogue which has a potentiality to fulfil the basic requirements for the scientists to minimize the burden of synthesis and represent a better molecule in all aspects. As we know the basic properties to justify molecular structure was its structure and electronic configuration which was directly related with the absorption profile of a molecule such as cytochrome P450 microsomal enzyme adaptivity as inhibitor or non inhibitor, Log P_{app}CaCO2 cell permeability, calculate its drug like property as Lipinski's rule of five as well as the bioactivity prediction as these molecules were associated with enzyme/ G-protein coupled receptor or ion/nuclear receptor and calculate toxicity parameter which justify the nature of the designed ligands. The other parameter as blood brain barrier penetration capacity was determined by using value of topological polar surface area, passive permeability factor (Log PS), partition coefficient value (Log P) and Log D, where Log D means distribution constant for any ionisable compounds as a function of pH.

2.Materials and Methods

2.1. Structural modification

Here the basic modifications was performed by enacting the basic stilbene functionalities and incorporation of a carbonyl group next to the stilbene double bond and the two phenyl group were modified by incorporating hydroxyl or amino group on the various position of phenyl or biphenyl moiety and finally designed a series of resveratrol analogue as (D1-D16) by using the Chemsketch ACDLAB software. These ligands were designed by maintaining the synthetic procedure to synthesize a basic chalcone moiety with a simple interaction of aromatic aldehyde and substituted acetophenone moiety.

2.2. Calculation of *in silico* physicochemical properties & Lipinski' Rule of Five

The *in silico* physicochemical properties of the designed structural analogue of resveratrol (D1-D16) were estimated by means of Log P_{app} (CaCo2 cell / Human Colonic Carcioma Cell Line permeability), Log P value (n-octanol/water partition co efficient), diffusion coefficient (D) by using the molinspiration online software. As well as the Lipinski' rule of five was estimated by the following characteristics as: The rule states, that most "drug-like" molecule have log P <= 5, molecular weight <= 500, number of hydrogen bond acceptors <= 10, and number of hydrogen bond donors <= 5. Molecules violating more than one of these rules may have problems with bioavailability. Finally the metabolism data was justified by the cytochrome P450 microsomal enzyme characteristics such as CYP 450 1A2, 2C9, 2D6, 2C19, 3A4.[12]

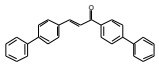
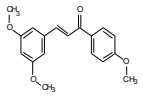
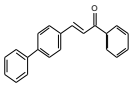
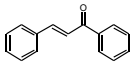
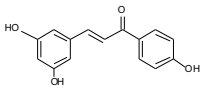
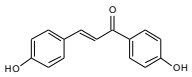
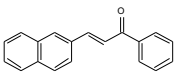
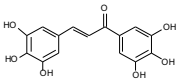
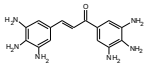
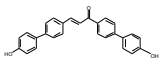
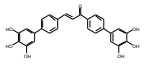
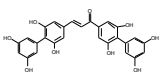
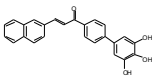
2.3.Prediction of *in silico* biological activity and toxicity parameter

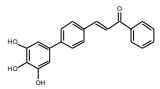
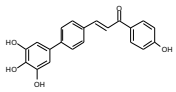
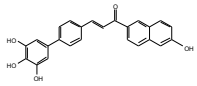
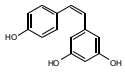
By using the molinspiration online software the mode of activity of the designed ligands (D1-D16) were predicted such as G-Protein Coupled Receptor (GPCR) type, Kinase inhibitor type, Nuclear receptor type, Protease inhibitor and Enzyme inhibitor type with respect to the standard resveratrol molecule as well as check their toxicity against human ether – a gogo cell, AMES toxicity test, carcinogenicity test and check it's in silico LD_{50} value against RAT model in mol/kg unit, toxicity against ER (Estrogen Receptor) or AR (Androgen Receptor), skin toxicity(TOX SKIN), respiratory tract toxicity (TOX RESP) and the MRTD data as Maximum Recommended Therapeutic Dose administered as an oral dose.[13]

2.4. Prediction of blood brain barrier permeability

The blood brain barrier permeability was estimated by three different ways as by using the PSA (polar surface area) value, the Log BB value (Blood Brain Barrier permeation) which was calculated using Log

Table 1. ADME prediction of Resveratrol analogues (D1-D16, Resveratrol)

Structure Code	Structure	Log P_{app} (cm/s) CaCo2 cell Permeability	LogD	MW (Mol.weight)	CYP 450 1A2 I (P)	CYP 450 2C9 I (P)	CYP 450 2D6 I (P)	CYP 450 2C19 I (P)	CYP 450 3A4 I (P)
D1.		2.0808	7.236	360.456	I (0.8017)	NI (0.7768)	NI (0.9626)	I (0.5412)	NI (0.9456)
D2.		1.5637	3.911	298.338	I (0.8501)	NI (0.9493)	NI (0.9377)	I (0.6090)	I (0.7738)
D3.		2.0808	5.413	284.358	I (0.8017)	NI (0.7768)	NI (0.9626)	I (0.5412)	NI ((0.9456)
D4.		2.1546	3.633	208.26	I (0.8366)	NI (0.7958)	NI (0.9438)	I (0.6760)	NI (0.9231)
D5.		1.0069	2.691	256.23	I (0.8996)	I (0.7000)	NI (0.9362)	I (0.7399)	I (0.9214)
D6.		1.4983	3.064	240.258	I (0.6525)	NI (0.5567)	NI (0.9506)	I (0.6890)	NI (0.5842)
D7.		2.0979	4.865	258.320	I (0.9146)	NI (0.9003)	NI (0.8451)	I (0.6881)	NI (0.8958)
D8.		0.4720	1.415	304.254	I (0.8928)	I (0.5111)	NI (0.9263)	NI (0.8768)	I (0.6787)
D9.		1.1943	0.483	298.350	I (0.8910)	NI (0.5476)	NI (0.8892)	NI (0.5123)	NI (0.5507)
D10.		1.4149	6.239	392.454	I (0.5971)	I (0.6229)	NI (0.9608)	I (0.6506)	NI (0.5939)
D11.		0.3787	5.055	456.450	I (0.8638)	I (0.6382)	NI (0.9432)	NI (0.8691)	I (0.6323)
D12.		1.0707	2.053	488.448	I (0.9142)	I (0.9100)	NI (0.9412)	I (0.8950)	I (0.7441)
D13.		0.3621	5.804	382.415	I (0.9082)	I (0.7146)	NI (0.9124)	NI (0.85510	I (0.6556)

Structure Code	Structure	Log P_{app} (cm/s) CaCo2 cell Permeability	Log D	MW (Mol.weight)	CYP 450 1A2 I (P)	CYP 450 2C9 I (P)	CYP 450 2D6 I (P)	CYP 450 2C19 I (P)	CYP 450 3A4 I (P)
D14.		0.3787	4.674	332.355	I (0.8639)	I (0.8639)	NI (0.9432)	NI (0.8691)	I (0.6323)
D15.		0.3787	4.162	348.354	I (0.8639)	I (0.8639)	NI (0.9432)	NI (0.8691)	I (0.6323)
D16.		0.3621	5.317	398.414	I (0.7146)	I (0.7146)	NI (0.8551)	NI (0.9082)	I (0.6556)
Resveratrol		1.1325	6.438	228.247	I (0.9106)	I (0.9106)	NI (0.9226)	I (0.8052)	I (0.7539)

P= Probability , I= Inhibitor, NI= Non-inhibitor

Table 2.Toxicity prediction of Resveratrol analogues (D1-D16, Resveratrol)

Structure Code	TOX MRTD	TOX ER Filter with LOG % RBA value	TOX AR Filter with LOG % RBA value	TOX SKIN	TOX RESP	TOX HERG with IC_{50} value in mol/l	AMES toxicity with probability value	Carcinogenicity with probability value	Rat acute toxicity LD_{50} value (mol/kg)
D1.	Below 3.16 (59%)	Toxic (78%) 0.1419	Toxic (77%) 9.791	Sensitizer (98%)	Sensitizer (73%)	Toxic 5.78	Non AMES toxic 0.9132	Non-carcinogens 0.5590	1.9553
D2.	Above 3.16 (96%)	Non Toxic (84%)	Toxic (67%) 0.0042	Nonsensit (71%)	Sensitizer (64%)	Non Toxic 5.03	Non AMES toxic 0.7397	Non-carcinogens 0.7426	2.1691
D3.	Above 3.16 (56%)	Toxic (68%) 0.0075	Toxic (81%) 2.1606	Sensitizer (98%)	Sensitizer (70%)	Toxic 5.53	Non AMES toxic 0.9132	Non-carcinogens 0.5590	1.9553
D4.	Above 3.16 (74%)	Toxic (71%) 0.0008	Toxic (75%) 0.0828	Sensitizer (98%)	Sensitizer (70%)	Toxic 5.10	Non AMES toxic 0.9132	Non-carcinogens 0.6105	1.7900
D5.	Below 3.16 (55%)	Toxic (71%) 0.05	Toxic (71%) 0.0032	Sensitizer (71%)	Sensitizer (64%)	Non Toxic 5.11	Non AMES toxic 0.8678	Non-carcinogens 0.8291	1.7253
D6.	Above 3.16 (58%)	Toxic (79%) 0.0106	Toxic (93%) 0.004	Sensitizer (71%)	Sensitizer (64%)	Non Toxic 5.05	Non AMES toxic 0.8931	Non-carcinogens 0.7981	1.3612
D7.	Above 3.16 (60%)	Toxic (69%) 0.0021	Toxic (81%) 3.7848	Sensitizer (98%)	Sensitizer (73%)	Toxic 5.6	Non AMES toxic 0.8931	Non-carcinogens 0.7468	2.1323

Structure Code	TOX MRTD	TOX ER Filter with LOG % RBA value	TOX AR Filter with LOG % RBA value	TOX SKIN	TOX RESP	TOX HERG with IC_{50} value in mol/l	AMES toxicity with probability value	Carcinogenicity With Probability value	Rat Acute Toxicity LD_{50} value (mol/kg)
D8.	Above 3.16 (56%)	Toxic (76%) 0.0070	Non Toxic (78%)	Sensitizer	Sensitizer (64%)	Non Toxic 4.46	Non AMES toxic 0.6630	Non-carcinogens 0.9041	1.9822
D9.	Above 3.16 (96%)	Toxic (69%) 0.6119	Toxic (75%) 13.6399	Sensitizer (98%)	Sensitizer (81%)	Non Toxic 4.71	AMES toxic 0.9259	Non-carcinogens 0.5118	2.3383
D10.	Below 3.16 (94%)	Toxic (96%) 2.6381	Toxic (93%) 1.6003	Sensitizer (90%)	Sensitizer (64%)	Toxic 5.98	Non AMES toxic 0.9250	Non-carcinogens 0.7580	1.4902
D11.	Below 3.16 (59%)	Toxic (96%) 0.5474	Toxic (93%) 6.6726	Sensitizer (98%)	Sensitizer (77%)	Non Toxic 5.84	Non AMES toxic 0.8415	Non-carcinogens 0.8801	2.0694
D12.	Below 3.16 (59%)	Toxic (96%) 4.7258	Toxic (67%) 0.0016	Sensitizer (98%)	Sensitizer (64%)	Non Toxic 4.42	Non AMES toxic 0.9702	Non-carcinogens 0.8311	2.0467
D13.	Below 3.16 (59%)	Toxic (96%) 0.0312	Toxic (69%) 20.3976	Sensitizer (98%)	Sensitizer (70%)	Toxic 6.06	AMES toxic 0.5332	Non-carcinogens 0.9152	2.2889
D14.	Below 3.16 (59%)	Toxic (96%) 0.0207	Toxic (68%) 9.0259	Sensitizer (98%)	Sensitizer (68%)	Toxic 5.58	Non AMES toxic 0.8415	Non-carcinogens 0.8801	2.0694
D15.	Below 3.16 (96%)	Toxic (96%) 0.0395	Toxic (67%) 7.4968	Sensitizer (98%)	Sensitizer (66%)	Toxic 5.46	Non AMES toxic 0.8415	Non-carcinogens 0.8801	2.0694
D16.	Below 3.16 (63%)	Toxic (96%) 0.1139	Toxic (68%) 17.5318	Sensitizer (98%)	Sensitizer (70%)	Toxic 5.84	Non AMES toxic 0.5332	Non-carcinogens 0.9152	2.2889
Resveratrol	Below 3.16 (56%)	Toxic (79%) 1.35943	Toxic (71%) 0.0047	Sensitizer (98%)	Sensitizer (64%)	Non Toxic 4.88	Non AMES toxic 0.8407	Non-carcinogens 0.7825	1.6791

MRTD = Maximum Recommended Therapeutic Dose administered as an oral dose.

Table 3. Bioactivity score of Resveratrol analogues (D1-D16, Resveratrol)

Structure Code	GPCR ligand	Ion channel ligand	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
D1.	-0.01	-0.05	-0.10	-0.00	-0.06	0.04
D2.	-0.14	-0.22	-0.29	-0.09	-0.27	-0.06
D3.	-0.03	-0.07	-0.15	-0.03	-0.13	0.05
D4.	-0.43	-0.18	-0.66	-0.51	-0.60	-0.12

Structure Code	GPCR ligand	Ion channel ligand	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
D5.	-0.16	-0.10	-0.34	-0.03	-0.36	0.05
D6.	-0.21	-0.07	-0.41	-0.13	-0.40	0.03
D7.	-0.11	-0.11	-0.28	-0.14	-0.23	0.04
D8.	-0.06	-0.07	-0.18	-0.01	-0.18	0.10
D9.	-0.08	-0.08	-0.10	-0.16	-0.12	0.13
D10.	0.03	-0.02	-0.06	-0.11	-0.04	0.08
D11.	0.01	-0.02	-0.03	-0.06	-0.06	0.10
D12.	0.07	-0.09	-0.05	0.19	-0.06	0.04
D13.	0.04	-0.01	-0.00	0.09	-0.04	0.10
D14.	0.01	-0.02	-0.04	0.07	-0.08	0.14
D15.	0.02	-0.01	-0.02	0.13	-0.07	0.14
D16.	0.06	0.00	0.04	0.16	-0.04	0.18
Resveratrol	-0.20	0.02	0.02	0.01	-0.42	0.02

BB=(-)0.0148PSA+0.152 Log P+0.139 [equation 1] and by passive permeability study as Log PS= (-) 2.712+ 0.312 Log D [equation 2]and try to find out a correlation in between various ways of blood barrier permeability calculation by taking twelve established CNS active molecules. By using the value of TPSA (Topological Polar Surface Area) which was previously calculated from molinspiration cheminformatics, the passive permeability was estimated[14] and tabulated in Table 4.

3.Results and Discussion

Among all the designed resveratrol analogues two molecular properties are the primary one as partition coefficient value and topological polar surface area which were solely based on the insertion of polar and non polar groups. Among the designed ligands D1, D3, D10, D13, D16 were violate the Lipinski rule of five which correlate that these molecule may have some problem with bioavailability. As per theTable 1 the value of CaCo2 cell permeability

Table 4. Blood brain barrier penetration parameter (BBB) score of Resveratrol analogues (D1-D16, Resveratrol)

Structure Code	PSA	LogP	LogBB	Log PS
D1.	17.071	7.402	1.011	-0.45
D2.	44.773	3.909	0.070	-1.48
D3.	17.071	5.606	0.738	-1.02
D4.	17.071	3.811	0.465	-1.57
D5.	77.755	2.302	-0.660	-1.87
D6.	57.527	2.853	-0.278	-1.75
D7.	17.071	4.995	0.645	-1.19
D8.	138.439	1.292	-1.710	-2.26
D9.	173.209	0.422	-2.360	-2.55
D10.	57.527	6.443	0.266	-0.763

Structure Code	PSA	LogP	LogBB	Log PS
D11.	138.439	4.882	-1.16	-1.13
D12.	178.895	4.176	-1.87	-2.06
D13.	77.755	5.530	-0.171	-0.899
D14.	77.755	4.347	-0.351	-1.25
D15.	97.983	3.868	-0.723	-1.41
D16.	97.983	5.027	-0.547	-1.051
Resveratrol	60.684	2.986	-0.305	-0.701
SR171416A	38.820	4.321	-0.0576	-0.360
Tiagabine	40.540	2.480	-0.084	-1.265
Amitriptyline	3.240	4.978	0.847	-1.160
Carbamazepine	46.330	2.562	-0.157	-1.294
Phenytoin	58.200	2.170	-0.392	-1.524
Valproic Acid	37.300	2.730	-0.00192	-1.944
Caffeine	61.820	0.063	-0.766	-2.152
Diazepam	32.670	2.881	0.0933	-1.273
Alprazolam	43.070	2.622	-0.099	-1.353
Gabapentin	63.320	0.622	-0.703	-1.626
Pentobarbitone	75.270	2.112	-0.653	-1.557
Theobromine	72.680	0.106	-0.5858	-2.700

of the standard resveratrol molecule (1.135) the designed molecules were with efficient values which corresponds with the better intestinal absorption as well as all of the designed ligands except D8, D9, D11, D13, D14, D15, D16 were inhibitor of CYP2C19 microsomal enzyme which were may be active against breast cancer cell line.[15]

In the case of Table 2 among the designed ligands D7, D9, D13 were AMES toxic and all were toxic against estrogen receptor and androgen receptor except D2 was nontoxic against estrogen receptor and D8 was nontoxic against androgen receptor. So it may be conclude that it may not be cause elevation of hormonal level and sensitize against skin and respiratory tract except D2 was not sensitize against skin. D2, D5, D6, D8, D9, D11, D12, resveratrol were non toxic against human ether a gogo K^+ cell, all were non carcinogenic as per the insilico data and D6 has the lowest LD50 value 1.3612 mol/Kg. In the case of Table 3 the bioactivity score tabulation, if the bioactivity score is more than 0.00 then it is active, if within -0.50 to 0.00 then it is moderately active, if less than -0.50 then inactive[16]. So among the designed ligands and standard resveratrol, the D1-D9, D11, D13-D16 were worked by theenzyme inhibition process followed by nuclear receptor and GPCR process, D10, D12 were worked by the nuclear receptor process and standard resveratrol was act by the ion channel receptor process.

For CNS active drug molecule Blood brain barrier penetration is the only physicochemical parameter has to be taken into consideration Table 4. In silico parameter like PSA, LogBB and LogPS for a CNS active agent are important to be evaluated weather they could cross BBB or not. PSA has been used as a predictor for BBB penetration by many investigators. In general, drugs aimed at the CNS tend to have lower polar surface areas than other classes. Polar Surface Area (PSA) for CNS penetration molecules was estimated at 60–70 $Å^2$ range. The upper limit for PSA for a molecule to penetrate the brain was around 90 $Å^2$. Result indicate that newly designed structure D1-D16 can cross BBB with their PSA value less than 90 $Å^2$ except D8, D9, D11, D12, D15, D16. Another important In silico parameter to identify CNS active agent is LogBB. For in silico prediction compound with Log BB value more than 0.3 is considered high absorption through BBB whereas between 0.3 to - 0.1 and less than -0.1 is considered to be moderate and less absorption through BBB. Result revealed that structure D1, D3, D4, D7 have high, structure D2, D5, D6, D10, D13, D14, D15, D16, resveratrol has moderate and structure D8, D9, D11, D12 has less BBB absorption chance. BBB permeability is often expressed as the BBB permeability-surface area product (PS, quantified as log PS). Unlike log BB, log PS is a direct measure of permeability and theoretically is not confounded by the plasma and brain tissue binding. Therefore, it may be a more relevant parameter to assess the brain penetration properties of a compound in drug

discovery. In present study we calculated Log PS value by using following equation (equation 1).[17] Result indicate that the there was a lowest level of Log PS value of the standard established molecule -0.36 of SR171416 and highest value of -2.7 with theobromine and the Log PS value of the designed ligands from D1-D16 and standard resveratrol molecule were fall from -0.45 to -2.55, which may be correspond with the development of potential CNS active agent. As previously there was a blurry concept of which drug can cross blood brain barrier or which cannot, but from this work a good correlation was coming out in between Log P and Log PS value as per Fig. 2 with r^2 value 0.7104 whereas in the case of Fig. 1 and Fig. 3 the relation in between PSA and Log BB with Log PS value represent a correlation value of 0.3918 and 0.5703 respectively.

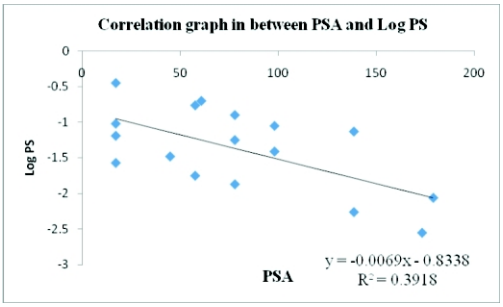


Fig.1. Correlation data in between PSA and Log PS $n=17, R^2= 0.3918$

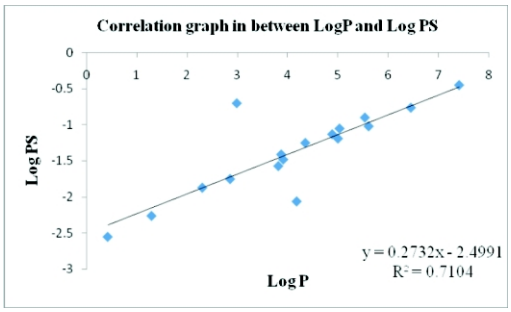


Fig.2. Correlation data in between Log P and Log PS $n=17, R^2= 0.7104$

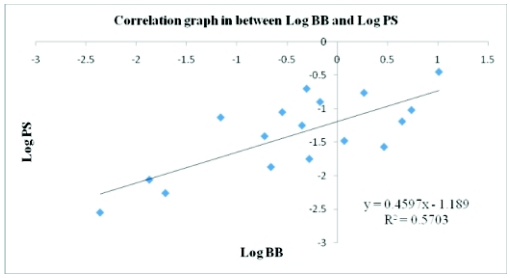


Fig.3. Correlation data in between Log BB and Log PS $n=17, R^2= 0.5703$

So in future if we consider Log PS value, we not only consider P-glycoprotein substrate capacity but also Log P value, by which we can deliver a set of good molecule with the ease in their activity profile.

4. Conclusion

In this present study, the designed ligands were tested in *in silico* way as intestinal absorption, partition coefficient, cytochrome P450 activity, various bioactivity profiling, various toxicity, if the molecules were suggested to concentrate on the central nervous system then the polar surface area, Log BB and Log PS value correlate with that purpose, which suggested that D1 showed better CNS penetrating activity, all the designed ligands showed similar toxicity profile. The bioactivity profile showed that the D14, D15, D16 showed betterbioactivity by the enzyme inhibitor process as well as a probability act by ion channel receptor so it can be worked against CNS and GPCR profiling also suggest the same. So, if the designed ligands were synthesized in future it may behave as a HIT. As well as there is a good correlation occurred in between Log P and Log PS with the r^2 value 0.7104 which can correlate with the brain penetration capacity of a molecule which can help us to consider Log P value as a primary one to correlate with Log PS (passive permeability factor).

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Conflicts of interest

The author reports no conflict of interest.

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